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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,919	10/26/2000	Martin Gerl	02481.1704	4319

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,919	GERL ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9 and 11-14* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 3/19/2004 has been received and entered into record and considered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-2, 4, 6-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pH level around 8.5 to about 9.0, does not reasonably provide enablement for any level. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> The instant invention directs to a process for detecting a C-peptide containing impurities in a sample of insulin or derivative by a non-radioactive assay. However, applicant stresses that "due to the physical properties of the test batch step samples, the antibodies used *must* interact with the antigens with sufficient affinity at a pH of about 8.5 - 9.0." (See page 3, third paragraph) Furthermore, working examples and other commercial assays compared by applicant also indicate that the pH of about 8.5 - 9.0 range is necessary for the instant invention. (See example 1, RIA kit, cat #HP1-15K at page 7) Accordingly, the scope of the current invention can operate at a limited pH level, namely pH of about 8.5 - 9.0, not at all pH level.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 6, line 5, "and" should change to "or" for correct Markush recitation.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-2, 6-9, 11-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iizuka et al. (Biomedical Research (1990) 11: 417-423) in view of Hara et al.(EP 0484961) and Newgard (US 5811266).

Iizuka et al. teach measuring human C-peptide containing sample by mixing the sample with a first antibody specifically recognizing the C-peptide, and a tracer, e.g. C-peptide,

and a second radioiodinated I^{125} antibody bead recognizing the first anti-C-peptide for determining the human C-peptide which is a degradation product from processing proinsulin. (See Abstract, Introduction, Materials and Methods).

However, Iizuka et al. do not teach (1) using recombinant human insulin as the sample, (2) non-radioactive assay to determine the C-peptide in a sample.

Newgard teaches using genetic recombinant method to produce human insulin to meet the great demand and research in diabetes. (Col 3, line 20-45; Claim 1)
Hara et al. teach labeling on antibodies recognizing the antibody specific for the C-peptide for an efficient assay. Hara et al. pointed out problems with radioactive safety of an operator and disposal of the isotope for immunoassay. (page 2, line 12-16) Therefore, Hara et al. also include an alternative labeling technique, namely non-radioactive fluorescence labeling. (page 2, line 28-55) The instant recited acridinium ester moiety for tracer in claim 9, is a kind of fluorescent substances encompassed by Hara et al. reference. (page 2, line 52-54) Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to have provided the assay of Iizuka et al. to detect the purity of the genetically produced human insulin as taught by Newgard for the great demand of human insulin and its quality control in diabetes research and labeling another antibody recognizing the first antibody specific for the C-peptide with a non-radioactive labeling as an alternative substitutes for radioactive I^{125}, for a safe operation and disposal.

8. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Iizuka, in view of Hara and Newgard, and further in view of Flora et al. (US 6444641).

Izuka, Hara, Newgard et al. references have been discussed but do not specifically teach perform the assay at a pH level around 8.5-9.0. Flora et al. disclose the solubility human C-peptide is around pH 8.02-9.0. (See Table 5) Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the

instant recited non-radioactive assay for detecting human C-peptide with an optimal pH level around 8.5-9.0, as taught by Flora et al. because it is known that certain pH level would be necessary, i.e. soluble condition, for performing immunoassay.

9. Claims 4 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iizuka Hara and Newgard, and further in view of Naithani et al.. (Fed. Rep. Ger. International Congress Series (1979) 468: 94-98)

Iizuka, Newgard and Hara et al. references have been discussed but do not disclose antibodies specifically recognizing monkey C-peptide. Naithani et al. teach syntheses of *monkey* C-peptide and its derivatives. (See abstract) It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the conventional antibody technique to generate antibody specific for monkey C-peptide because the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of monoclonal antibodies against it is *prima facie* obvious. See Ex parte Ehrlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. APp. & Int. 1990).

Response to Applicant's Arguments

10. Applicant's arguments with respect to claim 3 has been considered but are moot in view of the new ground(s) of rejection.

11. Claims 1-2, 6-9, 11-12 and 14 rejected under 35 U.S.C. 103(a) as being unpatentable over Iizuka et al. (Biomedical Research (1990) 11: 417-423) in view of Hara et al.(EP 0484961) and Newgard (US 5811266), are maintained.

Applicant cited *Winner v. Wang*, 53 USPQ 2d 1580, 1587 (Fed. Cir. 2000) in stressing the 103 obviousness rejection must be "desirable", not merely feasible, have been considered but are not persuasive. The above discussion provides motivation and

suggestions for combining all three references together. Examiner had outlined the underlined motivation, i.e. radio-safety concern and quality control, i.e. impurity from C-peptide, and clearly established prima facie obviousness. Taken together, the combination is not merely "feasible" but rather "desirable" to one skilled in the art under *Winner*.

Applicant further argues that Hara does not suggest any reason to use a non-radioactive label over a radioactive one. Applicant's argument has been considered but is not persuasive. Examiner had pointed out that Hara et al. reference had mentioning the safety concern on radioactive materials. Hara et al. indicate that both radiolabel and non-radiolabel are within the choices to one skilled in the art. (See page 2, fourth paragraph and last second paragraph)

Additionally, applicant argues that combining both Iizuka and Hara would in conflict because Hara et al. teach a microtiter-plate assay whereas Iizuka et al. using bead instead. Applicant's argument has been considered but is not persuasive. The main concern for Hara et al. reference is the safety of radio-contamination in using radiolabel materials for the assay. Since early 1980', one skilled in the art has been aware of this potential problem and diligently search for radioactive substitutes. Therefore, the suggestion or motivation provided by Hara et al. reference is to replace the I^{125} with non-radioactive material for the assay. Using non-radioactive labeling technique suggested by Hara et al. would not necessarily conflict the Iizuka et al. teachings.

Allowable Subject Matter

6. Claim 10 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

7. The following is an examiner's statement of reasons for allowance: no prior art teaches or suggests that using two antibodies detect human C-peptide where the presence of about 1 mg/ml human insulin does not interfere with the binding of the antibody specific for C-peptide.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-282-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

May 22, 2004

LONG V. LE
SUPERVISORY PATENT EXAMINER
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05/28/04